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Maternal cotyledons at birth predict blood pressure in childhood

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ABSTRACT

Introduction: A small placental surface at birth has been shown to be associated with the development of hypertension in later life. In this study we extend this observation by looking at the relationship between the number of placental cotyledons and blood pressure in childhood. Because the number of cotyledons is correlated with the surface area, we hypothesized that fewer cotyledons would be associated with higher blood pressure.

Methods: The Alspac study is a longitudinal study of 13,971 children born in Bristol. Their placentas were stored in formalin. We photographed the placentas of a sample of the children and related the number of maternal cotyledons to their blood pressure levels at age 9 years.

Results: Contrary to our hypothesis, a greater number of maternal cotyledons was associated with higher blood pressure. Among boys, a greater number of cotyledons was associated with higher systolic and diastolic pressure but not with higher pulse pressure. Diastolic pressure rose by 2.2 mmHg (95% CI 0.6 to 3.7, $p = 0.007$) for every 10 additional cotyledons. Among girls, a greater number of cotyledons was associated with higher systolic pressure and pulse pressure but not with higher diastolic pressure. Pulse pressure rose by 2.7 mmHg (1.1–4.3, $p < 0.001$) for every 10 additional cotyledons. These associations were little changed by adjustment for placental surface area.

Conclusion: Our study has shown that a large number of maternal cotyledons is associated with raised blood pressure in childhood. The associations differ in the two sexes.

1. Introduction

People whose birthweights were towards the lower end of the normal range have higher blood pressures as children and adults

minor variations in nutrient supply to different organs and systems during development permanently set the structure and function of the body. Birthweight is correlated with placental weight. Bigger babies generally have heavier placentas. Some studies have shown that hypertension in later life is related to low placental weight [4,5], while others have shown relationships with a high ratio of placental weight to birth weight [5,6]. Which of these two relationships occurs depends on the mother's height and socio-economic status [5]. The weight of the placenta, however, is a crude measure that does not distinguish the size of the surface from its thickness. Hyper-

placental

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ns on the placental surface and blood pressure in childhood. Our hypothesis was that fewer cotyledons, associated with a smaller placental surface, would be associated with raised blood pressure.

The maternal cotyledons, or lobes, of the placenta are on the maternal side of the surface [7]. Each cotyledon is a perfusion chamber partly or wholly separated from adjacent chambers by a wall of connective tissue, which may be lined by trophoblast cells. One or more maternal spiral arteries jet blood into the chamber. The fetal cotyledons comprise one or more fetal villous trees, containing a fetal artery and a vein, that are suspended into the maternal cotyledon. The number of maternal cotyledons in the placenta is highly variable. What determines the number is unknown, though it may depend on events in early gestation.

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Table 1
Characteristics of the study sample.

	Boys ($n = 421$)			Girls ($n = 489$)		
	Mean	SD	Missing	Mean	SD	Missing
Mother						
Height (cm)	164.5	6.5	21	164.5	7.0	19
Weight before pregnancy (kg)	62.1	10.5	29	61.5	10.3	36
Body mass index (kg/m^2)	23.0	3.8	30	22.7	3.8	40
Age (years)	29.4	4.5	0	28.8	4.3	1
Primiparous (%)	45.9	–	11	46.4	–	13
Newborn						
Weight (g)	3529	518	7	3422	445	4
Length (cm)	51.3	2.1	42	50.4	1.9	42
Head circumference (cm)	35.3	1.3	39	34.6	1.1	40
Gestation (weeks)	39.5	1.6	0	39.7	1.4	1
Placenta						
Weight (g)	553	112	1	546	99	0
Length (cm)	20.4	2.4	0	20.2	2.2	0
Width (cm)	17.8	2.0	0	17.7	1.8	0
Area (cm^2)	288	60	0	282	52	0
Thickness (cm)	2.8	0.5	0	2.8	0.5	0
Number of cotyledons	12.7	4.5	60	13.6	4.4	39
Child at age 9 years						
Age (years)	9.8	0.3	0	9.8	0.3	0
Height (cm)	139.8	6.3	4	139.4	6.3	11
Weight (kg)	34.4	7.0	0	35.3	7.6	1
Body mass index (kg/m^2)	17.5	2.7	4	18.1	3.0	11
Systolic blood pressure (mm Hg)	102.5	9.2	0	101.9	9.1	0
Diastolic blood pressure (mm Hg)	57.0	6.9	0	57.7	6.0	0
Pulse pressure (mm Hg)	45.5	7.6	0	44.3	7.9	0
Heart rate (beats/min)	76.6	10.1	0	80.4	10.7	0

2. Methods

ALSPAC is a longitudinal birth cohort study of the determinants of development, health, and disease during childhood and beyond [8]. Briefly, 14 541 pregnant women with an expected date of delivery between April 1991 and December 1992 were enrolled; 13 971 of their children formed the original cohort at 1 year of age. The pregnancies were selected irrespective of any complications that did or did not occur. The children have been repeatedly examined. The techniques used for blood pressure measurement have been described elsewhere [9]. In our study we have used blood pressure measurements and heart rates recorded at 9 years of age. After this age the adolescent growth spurt perturbs the tracking of blood pressure. The parents of each subject in the original study gave written informed consent. Ethical approval was granted by the ALSPAC Law and Ethics Committee and local research ethics committees.

At birth, the body size of the baby was measured. The length of gestation was estimated from the date of the mother's last menstrual period. The placenta was stored in 10% formalin. In our study, we photographed a sample of 1746 stored placentas. The placentas, which all came from one maternity hospital, were taken in the order in which they were stored. They were selected without any knowledge of the measurements made at birth or during the follow-up of the children. The placentas were removed from their containers, rinsed, trimmed using a standard protocol and weighed. The maternal and fetal side of each placenta was photographed using a digital camera. Each photograph included a ruler to measure the length and breadth of the surface. The length was defined as the maximum diameter and the breadth was measured at right angles to the midpoint of the length. Assuming an elliptical surface, the placental area was defined as the product of the length and breadth, multiplied by $\pi/4$. The number of maternal cotyledons was counted. With the maternal side upwards an incision was made in each quadrant and the thickness measured through the incision.

2.1. Statistical methods

We used multiple linear regression analysis to examine the relationship between placental measurements and blood pressure, pulse pressure and heart rate. Blood pressures rose with increasing body weight and we adjusted for this and for age in our analyses. Because we found differences in the associations among boys and girls we present separate analyses for the two sexes.

3. Results

There were 910 subjects, 421 boys and 489 girls, for whom there were measurements of blood pressure at age 9 years. Table 1 shows the characteristics of the mothers, newborn babies and the nine year old children. Girls were smaller than boys for each measurement of body size at birth and for each placental measurement, except for the number of maternal cotyledons. The number of cotyledons ranged from 3 to 37. On average girls had 0.7 more cotyledons than boys (95% confidence interval 0.3 to 1.2, $p = 0.001$).

Both systolic and diastolic pressure fell with increasing birth weight. Among boys mean systolic pressure fell by 2.0 mm (95% CI 0.5 to 3.5, $p = 0.008$) per kg increase in birth weight, while diastolic pressure fell by 1.0 mm Hg (−0.2 to 2.2, $p = 0.1$). The corresponding figures for girls were 3.0 (1.3–4.6, $p < 0.001$) and 1.7 (0.5–2.9, $p = 0.006$). These values were little changed by adjustment for gestational age at delivery, which was not associated with blood pressure.

3.1. Number of cotyledons

Heavier birthweight was associated with a greater number of cotyledons. A one kg increase in birth weight was associated with a 1.3 (95% CI 0.6 to 1.9, $p < 0.001$) increase in the mean number of cotyledons among boys, and a 0.8 (0.1–1.5, $p = 0.03$) increase among girls. The number of cotyledons was positively related to the surface area. Every 100 cm^2 increase in area was associated with a 1.7 (1.1–2.2, $p < 0.001$) increase in the average number of cotyledons among boys, and a 2.2 (1.6–2.8, $p < 0.001$) increase among girls. The number of cotyledons was not independently related to any other placental measurement.

Table 2 shows the relationship between placental size and blood pressure and heart rate. Among boys a greater number of cotyledons was associated with higher systolic and diastolic pressure, but not with higher pulse pressure or heart rate. Among girls a greater number of cotyledons was associated with higher systolic and pulse

Table 2
Correlation coefficients of placental size with blood pressure and heart rate.

Placental measurement	Systolic blood pressure		Diastolic blood pressure		Pulse pressure		Heart rate	
	Correlation	*p*-Value	Correlation	*p*-Value	Correlation	*p*-Value	Correlation	*p*-Value
Boys								
No. cotyledons	0.12	0.03	0.14	0.007	−0.01	0.9	−0.02	0.7
Length	−0.10	0.05	−0.05	0.3	−0.06	0.2	−0.01	0.8
Width	−0.03	0.5	−0.03	0.6	−0.01	0.9	0.02	0.6
Weight	−0.04	0.4	−0.10	0.05	0.04	0.4	0.05	0.3
Girls								
No. cotyledons	0.09	0.05	−0.08	0.1	0.16	<0.001	0.09	0.05
Length	−0.05	0.2	−0.11	0.01	0.03	0.5	−0.02	0.6
Width	−0.05	0.2	−0.11	0.02	0.03	0.6	0.01	0.9
Weight	−0.04	0.4	−0.04	0.4	−0.01	0.9	0.00	0.9

Table 3
Mean blood pressures and heart rates according to number of maternal cotyledons.

No. cotyledons	Systolic blood pressure (mm Hg 95% CI)	Diastolic blood pressure (mm Hg)	Pulse pressure (mm Hg)	Heart rate (beats/min)	No. children
Boys					
−8	101.3	55.7	45.6	77.8	65
9–11	101.8	56.5	45.3	75.9	94
12–14	103.6	57.5	46.1	77.0	79
15–17	103.6	57.4	46.2	77.1	69
18+	103.2	58.8	44.3	76.3	54
p for trend	0.05	0.007	0.7	0.7	
mm Hg per 10 cotyledons	1.9 (0.0–3.7)	2.2 (0.6–3.7)	−0.3 (−2.0 to 1.3)	−0.5 (−2.9 to 1.9)	
Girls					
−8	100.2	58.7	41.4	76.8	55
9–11	101.5	57.7	43.8	81.6	86
12–14	101.9	57.4	44.5	80.0	128
15–17	103.3	58.2	45.1	82.3	103
18+	102.2	56.3	45.9	80.3	77
p for trend	0.05	0.1	<0.001	0.05	
mm Hg per 10 cotyledons	1.7 (0.0–3.4)	−1.0 (−2.3 to 0.2)	2.7 (1.1–4.3)	2.2 (−0.1 to 4.5)	

pressure, and higher heart rate, but not with higher diastolic pressure. The trends with the number of cotyledons in boys and girls are shown in Table 3. The trends in diastolic pressure and pulse pressure were statistically significantly different in the two sexes (p for interaction = 0.002 and 0.02).

3.2. Placental surface

There were different associations between the length and breadth of the placental surface and later blood pressure in the two sexes (Table 2). Among boys greater length of the placental surface was associated with lower systolic pressure. Among girls, greater length, breadth and area of the placental surface were associated with lower diastolic pressure. In simultaneous regressions with length, breadth or area, the effects of number of cotyledons on blood pressure were little changed. The thickness of the placenta was not associated with blood pressure in either sex.

4. Discussion

Contrary to our hypothesis, we found that a greater number of maternal cotyledons at birth was associated with higher blood pressure at 9 years of age. The associations differed in the two sexes. Among boys, a greater number of cotyledons was associated with higher systolic and diastolic pressure but not with higher pulse pressure. Among girls, a greater number of cotyledons was associated with higher systolic pressure and pulse pressure but not with higher diastolic pressure.

As expected from many other studies of blood pressure in childhood [1], we found that lower birthweight was associated with higher systolic and diastolic blood pressure. Although placentas with a larger surface area had more cotyledons, raised blood pressure was associated with a smaller length, breadth or area of the placental surface. This is consistent with findings linking a small placental surface to later hypertension [4]. The association between cotyledon number and blood pressure was little changed by allowing for the size of the surface. This suggests that the processes that link greater cotyledon number to raised blood pressure differ from those that link small surface area to raised blood pressure.

Our thesis is that cotyledon number is linked to settings in the fetal autonomic nervous system while area is linked to nutrient supply. A placenta with a large number of cotyledons will have more walls of connective tissue separating the cotyledons. This tissue is not involved in nutrient exchange but will have a continuing demand for nutrients in order to maintain itself. We speculate that, for whatever reason, this is associated with increased stress to the fetus, leading to altered settings of the autonomic nervous system that increase vascular tone. Persistence of increased vascular tone after birth leads to raised blood pressure. Another possible explanation for the link between cotyledon number and later blood pressure is that it reflects an altered structure of the villous vascular tree. Boys and girls grow differently in utero [10], and there are sex differences in the associations between cotyledon number and blood pressure.

Systolic blood pressure is determined by stroke volume, vascular stiffness and peripheral resistance. Diastolic pressure is determined by stroke volume, peripheral resistance and heart rate. Pulse pressure is determined by stroke volume heart rate and peripheral resistance. A larger number of cotyledons among boys predicted raised systolic and diastolic pressure and we infer that boys with a larger number of cotyledons have increased peripheral resistance as a result of increased sympathetic tone. A larger number of placental cotyledons among girls predicted raised systolic and pulse pressure but not diastolic pressure. More cotyledons in girls was also associated with higher heart rate. The association with raised pulse pressure cannot therefore be attributed to an association with reduced heart rate. We infer that girls with larger number of cotyledons have an imbalance in the autonomic nervous system such that the balance of sympathetic to parasympathetic tone is increased. There may, however, be other explanations.

4.1. Limitations of the study

Our study is based on one population in Southern England and the findings may not be generalizable to other places. We are therefore seeking to replicate them in another country. The number of cotyledons in our sample ranged from 3 to 37, which is wider than ranges previously cited [11]. Although blood pressure levels are known to track through childhood into adult life, the long term significance of differences in childhood blood pressure will need to be established through the continued follow-up of the ALSPAC cohort.

4.2. Conclusion

Our study has shown, for the first time, that a large number of maternal cotyledons is associated with a raised blood pressure in childhood. The associations are different in the two sexes. We speculate that they reflect altered settings of the autonomic nervous system.

Acknowledgments

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